Prevalence and characteristics of the metabolic syndrome in 2479 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis

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Abstract

Objective: An increased risk of cardiovascular morbidity and mortality in adult GH deficiency (GHD) may be related to hypopituitarism but also to the presence of the metabolic syndrome (MetS). Our objective was to investigate the characteristics and prevalence of MetS as well as its comorbidities in adult GHD.

Design: In KIMS (Pfizer International Metabolic Database) 2479 patients with severe adult-onset GHD, naïve to GH replacement, with complete information on all MetS components were found. MetS was defined according to the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP) and the International Diabetes Foundation (IDF).

Methods: The prevalence of MetS was calculated and compared with previously published data from the normal population. Associations were assessed between background variables, baseline variables, comorbidities, and MetS.

Results: MetS was present in 43.1% (NCEP) and in 49.1% (IDF) of patients, clearly higher than data from the normal population (20–30%). MetS prevalence was related to age, GHD duration, and body mass index (BMI), but not to GHD severity, extent of hypopituitarism, or etiology of pituitary disease. Adjusted for age, gender, and BMI, patients with MetS had a higher prevalence ratio for diabetes mellitus: 4.65 (95% confidence interval (CI): 3.29–6.58), for cardiovascular morbidity: 1.91 (95% CI: 1.33–2.75), and for cerebrovascular morbidity: 1.77 (95% CI: 1.09–2.87) than patients without MetS.

Conclusions: MetS is highly prevalent in GHD and is associated with a higher prevalence ratio for comorbidities. The presence of MetS in GHD may therefore contribute to the increased risk of cardiovascular morbidity and mortality found in these patients.

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Introduction

As a result of increased cardiovascular and cerebrovascular morbidity, mortality is increased in hypopituitary patients on conventional hormone substitution without GH replacement (1–6). Although existing evidence is confounded by simultaneous deficiencies of other pituitary hormones and the variability in their replacement, GH deficiency (GHD) is considered to play a certain role since it is characterized by an adverse profile in cardiovascular risk factors (7, 8).

The metabolic syndrome (MetS) finds its origin in the clustering of risk factors inducing both diabetes mellitus and cardiovascular risk factors, such as abdominal obesity, elevated blood pressure, hyperglycemia, hypertriglyceridemia, and decreased serum high-density lipoprotein (HDL)-cholesterol levels (9, 10). Several definitions to characterize MetS have been proposed, combining the same components with specific modifications. The National Cholesterol Education Program’s Adult Treatment Panel III (NCEP), and, to a lesser degree, the International Diabetes Federation (IDF) definitions are most widely used. MetS has been presented as a potential model to predict the development of diabetes mellitus and cardiovascular complications, but has also been criticized for not achieving this goal consistently, in part due to the imperfection of the current components (11).

The first aim of the present analysis was to study the prevalence and characteristics of MetS in patients with adult-onset GHD naïve to GH replacement. The second aim was to determine the prevalence of diabetes mellitus
and cardiovascular and cerebrovascular diseases in GHD in relation to the presence of MetS. The data in this analysis were retrieved from KIMS (Pfizer International Metabolic Database) (12).

Patients and methods

Patients

Patients were included in the analysis when they presented with severe adult-onset GHD confirmed by an accepted GH stimulatory test (13), naïve to GH replacement, and without medical history of acromegaly or Cushing’s disease. A total of 2479 patients with a mean age of 49.5 ± 13.0 years were included in the analysis. Males numbered 1274 (51.4%; mean age, 50.6 ± 12.8 years) and females 1205 (48.6%; mean age 48.3 ± 13.0 years). Isolated GHD was present in 8.9% of patients. All patients were Caucasians from 20 European countries and from Argentina. The study was performed in accordance with The Declaration of Helsinki (14).

Methods

Clinical data

Background data including gender, age, country of origin, smoking habits, etiology of hypopituitarism, previous pituitary or brain irradiation, extent of hypopituitarism (expressed as the number of pituitary hormone deficits additional to GH), estimated duration of GHD, history of diabetes mellitus and cardiovascular, and cerebrovascular diseases, as well as clinical data including body mass index (BMI), blood pressure, and waist circumference were retrieved from the KIMS database.

Biochemical data

Serum lipids and insulin-like growth factor 1 (IGF1) were measured centrally. Serum concentrations of total cholesterol (15), HDL-cholesterol (16), and triglycerides (17) were measured directly and performed in the same central laboratory. Serum IGF1 analyses were performed at Kabi Pharmacia, Stockholm, Sweden between 1994 and October 1997 and thereafter at Sahlgrenska University Hospital, Gothenburg, Sweden, using an RIA acid/ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA) until November 2002, a chemiluminescence immunoassay (Nichols Advantage System) until September 2006, and currently the Immulite 2500 (DPC Siemens, Deerfield, IL, USA) (18). IGF1 data are presented as SDS. The reference range ± 2 SDS was calculated from an age corrected algorithm in which IGF1 was expressed in μg/l. The algorithm formula used between 1994 and 1997 was: SDS = (ln (IGF1)−(5.95−0.0197×Age))/0.282; between 1997 and 2002: SDS = (ln (IGF1)−(5.92−0.0146×Age))/0.272, and from 2002 data from Brabant et al. (19).

All central analyses were performed on blood samples that were routinely obtained. Plasma glucose was measured locally and reported.

Definitions of MetS

The NCEP definition was used with minor modifications as pointed out hereby (20). Three out of following five components are required to retain the diagnosis of MetS:

- Waist circumference ≥ 102 cm for males and ≥ 88 cm for females.
- Hypertension indicated by a blood pressure > 130/85 mmHg, or the use of any antihypertensive drug.
- Serum HDL-cholesterol < 40 mg/dl (< 1.0 mmol/l; converting factor: 1 mg/dl = 0.0259 mmol/l) for males or < 50 mg/dl (< 1.3 mmol/l) for females, or the use of any lipid-lowering drug.
- Serum triglycerides ≥ 150 mg/dl (≥ 1.7 mmol/l; converting factor: 1 mg/dl = 0.0113 mmol/l), or the use of any lipid-lowering drug.
- Hyperglycemia indicated by a fasting plasma glucose ≥ 100 mg/dl (≥ 5.6 mmol/l) or a non-fasting plasma glucose ≥ 200 mg/dl (≥ 11.1 mmol/l), or a serum hemoglobin A1c ≥ 6.5%, or a previous diagnosis of diabetes mellitus, or the use of any anti-diabetic drug. The diagnosis of diabetes mellitus was accepted using the same parameters, except for a fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l).

For comparison with the NCEP definition, the IDF definition of MetS was also used with minor modifications as pointed out hereby (21). A waist circumference ≥ 94 cm for males and ≥ 80 cm for females is a mandatory component for the presence of MetS. In addition, two out of four remaining components already outlined in the NCEP definition are required for the diagnosis of MetS. Information according to the IDF definition will be reported separately and limited to a comparison with the NCEP data.

The patients were categorized into two groups depending on the absence (noMetS) or presence (MetS) of MetS. Using the NCEP definition, the noMetS group consisted of three categories: noMetS-0 (one combination without component), noMetS-1 (five combinations of an isolated component), and noMetS-2 (ten combinations of the two components), while the MetS group also consisted of three categories: MetS-0 (ten combinations of the three components), MetS-1 (five combinations of the four components), and MetS-2 (one combination of all five components).

Statistical analysis

Differences in mean between MetS and noMetS were analyzed using covariance analyses. Adjustment was
done for age and gender, and in some analyses for BMI. Studied mean differences were: duration of GHD, BMI (when not a nuisance variable), waist circumference, systolic and diastolic blood pressure, total and HDL-cholesterol, triglycerides, and IGF1 SDS. Results were presented with mean difference between MetS and noMetS and a 95% confidence interval (CI) and a P value.

Linear trend statistics in which the estimated change in mean over MetS index value (i.e. over zero to five components) were analyzed with adjustment for age and gender using linear regression analysis for variables as listed above. Results were presented with estimated linear change per index value (Δ) and 95% CI and a P value.

A positive predictive value was calculated as a percentage of patients with MetS in a given category (abnormal/normal) of an individual component of the MetS. It can be interpreted as the probability of having the MetS given the value of the individual component.

Analyses assessing prevalence and prevalence ratios of the MetS by some selected potential covariates were conducted using multiple log-linear Poisson working regression models with model-robust standard error estimates (22). Studied covariates were duration of GHD, irradiation, number of additional pituitary deficiencies, BMI, waist circumference, and IGF1 SDS. Prevalence and prevalence ratios of diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases by MetS groups were also studied. Estimates and 95% CI were likelihood based. Adjustments were done for age, gender, and BMI or by age and gender in case BMI was the main covariate. SAS v8.2 Proc Genmod (SAS Inc., Cary, NC, USA) was used for robust Poisson regression analyses.

### Results

#### Prevalence of MetS

According to NCEP criteria, 43.1% (1069/2479) of the GHD cohort fulfilled the definition of MetS. Details on gender, age, BMI, and waist for the MetS and noMetS groups are given in Table 1.

#### Relation of MetS groups to background variables

- Gender: MetS prevalence was similar in females and males (Table 1). MetS prevalence ratio for gender was 1.06 (95% CI: 0.97–1.14; P = 0.23).
- Age: MetS prevalence was related to age categories in both genders (Fig. 1a).
- Country of origin: MetS prevalence was between 38 and 48%, except for France (52%) and Spain (60%).
- Smoking habits: regular smoking (17.2% in MetS group vs 19.5% in noMetS group; P < 0.15).
- Etiology of hypopituitarism: MetS prevalence was highest in craniopharyngiomas (45.9%), pituitary adenomas (44.7%), and idiopathic/congenital GHD (42.4%).
- Cranial irradiation: radiotherapy did not influence MetS prevalence (44.8% in MetS group vs 43.1% in noMetS group; P = 0.29).
- Number or type of pituitary deficiencies: MetS prevalence was not influenced by the extent or type of hypopituitarism and was not different in patients with isolated GHD (44.1%).
- Duration of GHD (adjusted for age, gender, and BMI): MetS prevalence was significantly influenced by GHD

#### Table 1 Characteristics of MetS vs noMetS according to NCEP criteria.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MetS</th>
<th></th>
<th></th>
<th>noMetS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
</tr>
<tr>
<td>Total cohort (n (%))</td>
<td>537 (42.2)</td>
<td>532 (44.1)</td>
<td>1069 (43.1)</td>
<td>737 (57.8)</td>
<td>673 (55.9)</td>
<td>1410 (56.9)</td>
</tr>
<tr>
<td>Age (years; mean ± S.D.)</td>
<td>52.6 ± 11.5</td>
<td>52.1 ± 12.8</td>
<td>52.4 ± 12.2</td>
<td>49.1 ± 13.5</td>
<td>45.4 ± 12.4</td>
<td>47.3 ± 13.1</td>
</tr>
<tr>
<td>BMI (kg/m²; mean ± S.D.)</td>
<td>31.7 ± 4.2</td>
<td>31.9 ± 6.1</td>
<td>31.8 ± 5.2</td>
<td>27.0 ± 4.0</td>
<td>26.8 ± 5.2</td>
<td>26.9 ± 4.6</td>
</tr>
<tr>
<td>WC (cm; mean ± S.D.)*</td>
<td>109.4 ± 11.1</td>
<td>102.3 ± 12.9</td>
<td>102.2 (101.7–102.6)</td>
<td>97.0 ± 10.9</td>
<td>88.1 ± 12.2</td>
<td>98.8 (98.4–99.2)</td>
</tr>
<tr>
<td>Above target (%)</td>
<td>87.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33.1</td>
</tr>
<tr>
<td>Blood pressure adj mean (mmHg, 95% CI)*</td>
<td>135.1 (134.0–136.1)</td>
<td>83.2 (82.5–83.8)</td>
<td>60.9</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.38 (1.36–1.40)</td>
</tr>
<tr>
<td>SBP</td>
<td>135.1 (134.0–136.1)</td>
<td>83.2 (82.5–83.8)</td>
<td>60.9</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.38 (1.36–1.40)</td>
</tr>
<tr>
<td>DBP</td>
<td>135.1 (134.0–136.1)</td>
<td>83.2 (82.5–83.8)</td>
<td>60.9</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.38 (1.36–1.40)</td>
</tr>
<tr>
<td>Above target (%)</td>
<td>81.5</td>
<td>2.95 (2.84–3.05)</td>
<td>92.8</td>
<td>30.4</td>
<td>30.4</td>
<td>30.4</td>
</tr>
<tr>
<td>HDL-cholesterol, adj mean (mmol/l, 95% CI)*</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.38 (1.36–1.40)</td>
</tr>
<tr>
<td>Below target (%)</td>
<td>81.5</td>
<td>2.95 (2.84–3.05)</td>
<td>92.8</td>
<td>30.4</td>
<td>30.4</td>
<td>30.4</td>
</tr>
<tr>
<td>Triglycerides, adj mean (mmol/l, 95% CI)*</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.05–1.09)</td>
<td>1.38 (1.36–1.40)</td>
</tr>
<tr>
<td>Above target (%)</td>
<td>81.5</td>
<td>2.95 (2.84–3.05)</td>
<td>92.8</td>
<td>30.4</td>
<td>30.4</td>
<td>30.4</td>
</tr>
</tbody>
</table>

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; Adj mean, mean adjusted for age, gender, and BMI. *Indicates P < 0.0001 between MetS and noMetS.
duration: 2.13 years (95% CI: 1.91–2.36) in MetS vs 1.72 years (95% CI: 1.51–1.93) in noMetS (P = 0.012). MetS prevalence was < 44% with GHD duration < 2 years, 46.0% with GHD duration between 2 and 5 years, and 49.6% with GHD duration of more than 5 years. A trend in prolonged duration of GHD over escalating MetS categories was observed (P = 0.021; Table 2). MetS prevalence ratio for duration categories, measured after adjustment for age, gender, and BMI, is shown in Table 2 (P < 0.01 over categories). The increase in prevalence ratio by duration category is also shown in Table 2.

- **BMI:** MetS prevalence was related to BMI categories in both genders (Fig. 1b). It reached 75% in the highest BMI categories. MetS prevalence ratio for BMI categories, measured after adjustment for age and gender, is shown in Table 2 (P < 0.0001 over BMI categories). The increase in prevalence ratio by BMI category is also shown in Table 2.

- **Serum cholesterol (adjusted for age, gender, and BMI):** there was no significant difference between MetS (5.85 mmol/l, 95% CI: 5.76–5.93) and noMetS groups (5.87 mmol/l, 95% CI: 5.79–5.94; P = 0.73). No relation was observed between total cholesterol and escalating MetS categories (data not shown, P = 0.54).

- **Serum IGF1 SDS (adjusted for age, gender, and BMI):** MetS prevalence was not influenced by the severity of GHD expressed as IGF1 SDS: 1.54 (95% CI: 1.64 to 1.44) in the MetS group vs 1.63 (95% CI: 1.72 to 1.54) in the noMetS group (P = 0.23). A relationship between IGF1 SDS and escalating MetS categories was not found (data not shown, P = 0.31).

**Influence of MetS components**

- The target values for waist circumference, blood pressure, serum HDL-cholesterol, serum

**Table 2** MetS prevalence ratio according to NCEP criteria and IDF criteria, adjusted for age, gender, BMI.

<table>
<thead>
<tr>
<th>GHD duration categories</th>
<th>NCEP</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months (reference)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3–10 months</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>10–24 months</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2–5 years</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>By duration category (95% CI)</td>
<td>1.04 (1.01–1.08)</td>
<td>1.04 (1.01–1.07)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI categories (kg/m²)</th>
<th>NCEP</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25 (reference)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>25–30</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>30–35</td>
<td>4.2</td>
<td>3.6</td>
</tr>
<tr>
<td>35–40</td>
<td>5.2</td>
<td>4.3</td>
</tr>
<tr>
<td>&gt;40</td>
<td>6.0</td>
<td>4.2</td>
</tr>
<tr>
<td>By BMI category (95% CI)</td>
<td>1.51 (1.46–1.56)</td>
<td>1.39 (1.35–1.44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WC categories (cm)</th>
<th>NCEP</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;94 M/&lt;80 F</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>94–98 M/80–84 F</td>
<td>1.2</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>98–102 M/84–88 F</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>102–106 M/88–92 F</td>
<td>4.9</td>
<td>1.3</td>
</tr>
<tr>
<td>106–110 M/92–96 F</td>
<td>5.2</td>
<td>1.4</td>
</tr>
<tr>
<td>110–114 M/96–100 F</td>
<td>6.0</td>
<td>1.7</td>
</tr>
<tr>
<td>&gt;114 M/&gt;100 F</td>
<td>5.4</td>
<td>1.7</td>
</tr>
<tr>
<td>By WC category (95% CI)</td>
<td>1.32 (1.28–1.36)</td>
<td>1.11 (1.09–1.14)</td>
</tr>
</tbody>
</table>

WC, waist circumference; M, males; F, females.
triglycerides, and plasma glycemria were more frequently exceeded in the MetS group (Table 1). When adjusted for age, gender, and BMI, a significant difference was found between MetS and noMetS groups regarding waist circumference, blood pressure, serum HDL-cholesterol, and serum triglycerides ($P<0.0001$; Table 1).

- With increasing waist circumference, MetS prevalence also increased significantly for both genders ($P<0.0001$; Fig. 1c). MetS prevalence ratio for waist circumference categories, measured after adjustment for age, gender, and BMI, is shown in Table 2 ($P<0.0001$ over categories). The increase in prevalence ratio by waist circumference category is also shown in Table 2.

**Comorbidities in MetS**

- Diabetes mellitus: the prevalence was significantly higher in the MetS group, for the whole cohort (16.9 vs 3.0%; $P<0.0001$), for males (16.2 vs 2.7%; $P<0.0001$), and for females (17.7 vs 3.3%; $P<0.0001$). The prevalence of diabetes significantly increased with escalating number of components ($P<0.0001$), with a similar distribution by gender (Fig. 2a). With adjustment for age, gender, and BMI, prevalence ratio for diabetes mellitus in the MetS group vs in the noMetS group was 4.65 (95% CI: 3.29–6.58; $P<0.0001$).

- Cardiovascular morbidity: the prevalence was significantly higher in the MetS group, for the whole cohort (9.2 vs 3.4%; $P<0.0001$), for males (11.7 vs 4.0%; $P<0.0001$), and for females (6.6 vs 2.8%; $P=0.002$). The prevalence of cardiovascular morbidity also increased significantly with escalating number of components ($P<0.0001$). Conversely, in females where the cardiovascular morbidity was only outspoken in MetS-5, in males there was a progressive increase from MetS-3 onwards (Fig. 2b). With adjustment for age, gender, and BMI, prevalence ratio for cardiovascular morbidity in the MetS group vs the noMetS group was 1.91 (95% CI: 1.33–2.75; $P=0.0004$).

- Cerebrovascular morbidity: the prevalence was significantly higher in the MetS group, for the whole cohort (4.9 vs 2.3%; $P<0.0006$), for males (5.4 vs 2.7%; $P<0.014$), and for females (4.3 vs 1.9%; $P=0.016$). The prevalence of cerebrovascular morbidity also significantly increased with escalating number of components ($P=0.0025$). While in females the increase is gradual, in males the increase is pronounced from MetS-4 onwards (Fig. 2c). With adjustment for age, gender, and BMI, prevalence ratio for cerebrovascular morbidity in the MetS group vs the noMetS group was 1.77 (95% CI: 1.09–2.87; $P=0.022$).

**IDF analysis**

Due to the less stringent criterion for waist circumference in the NCEP definition, the prevalence of MetS according to the IDF definition was 6% higher than according to the NCEP definition: 49.1% ($n=1218/2479$) vs 43.1%. Gender distribution, age and BMI were similar for both analyses, while the occurrence of abnormalities in blood pressure, HDL-cholesterol, triglycerides, and hyperglycemia were comparable. The increased IDF prevalence compared with the NCEP prevalence was observed for each background variable. MetS prevalence ratio for GHD
duration categories, BMI categories, and waist circumference categories are shown in Table 2 (P=0.0001 over categories).

Prevalence of comorbidities was significantly higher in the MetS group compared with the noMetS group: 14.7 vs 3.5% (P<0.0001) for diabetes mellitus, 8.3 vs 3.6% (P<0.0001) for cardiovascular morbidity, and 4.3 vs 2.6% (P=0.024) for cerebrovascular morbidity. Prevalence ratio for comorbidities was also significantly higher in the MetS group for diabetes mellitus (3.28, 95% CI: 2.37–4.55; P<0.0001) for cardiovascular morbidity (1.73, 95% CI: 1.20–2.47; P=0.00029), but not for cerebrovascular morbidity (1.37, 95% CI: 0.86–2.19; P=0.19).

Discussion
This study confirmed the assumption that MetS is highly prevalent in hypopituitary patients with GHD of adult-onset, as a prevalence of 43.1% according to the NCEP definition and of 49.1% according to the IDF definition was found. Numerous studies to determine the MetS prevalence in the global population have been performed, but results depended primarily on the MetS definition (11). The prerequisite of central obesity, measured as waist circumference, makes the IDF definition less restrictive than the NCEP definition and leads usually to a higher prevalence, as also observed in this analysis (23). The composition of the population studied also impacts largely on the prevalence due to differences in gender, age, and ethnicity. To obtain an as homogeneous as possible cohort, it was decided to restrict the inclusion for this study to Caucasian patients with adult-onset GHD.

In a comparative US population study MetS prevalence was lately estimated at 34.5% (33.7% in males and 34.1% in females) based on the NCEP definition and at 39.0% (39.9% in males and 38.1% in females) based on the IDF definition (24). Recent European studies have demonstrated a lower MetS prevalence compared with the US data. A study performed in a cohort of 10 269 subjects from nine European countries estimated the NCEP prevalence at 30.2% (32.2% in males and 35.4% in females) and the IDF prevalence at 31.5% (32.7% in males and 28.5% in females) (25). A Swedish study in 5047 subjects found an NCEP prevalence of 20.7% (26.0% in males and 15.4% in females) and an IDF prevalence of 21.9% (27.9% in males and 17.9% in females) (26), while in a Norwegian study of 10 206 patients the NCEP prevalence was 25.9% (26.8% in males and 25.0% in females) and the IDF prevalence 29.6% (29.0% in males and 30.3% in females) (27). The DECODE study, which presented data on 9140 European subjects from eight countries, estimated the NCEP prevalence at 23.7% in males and at 23.1% in females (25). Although a strict comparison between the present study and normative data from the literature cannot be made, it may be assumed that MetS prevalence in GHD is about 15–20% higher than in the general population.

The high MetS prevalence in GHD could have been anticipated from the physiological lipolytic and anabolic actions of GH. The clinical and biochemical characteristics of GHD are now well recognized and have recently been described in detail in a large group of patients, reporting extensively on the five MetS components (28). The possible role of GH in the occurrence of MetS has been studied in severe obesity associated with functional GHD (29). Patients with a deficient GH response to GHRH plus arginine stimulation showed according to the NCEP definition a higher MetS prevalence compared with patients with a normal GH secretion (70.9 vs 52.9%; P<0.022), suggesting GHD to be an independent factor in the development of MetS.

One controlled study has addressed the occurrence of MetS in GHD (30). A group of 50 GHD patients was compared with an age-, gender-, and BMI-matched group of 1062 healthy controls. There was a more than twofold increase in MetS in the GHD group (38.0 vs 15.7%; P<0.0001). Neither age, gender, GHD etiology, GHD duration nor pituitary irradiation determined the presence of MetS. Main differences with this study were the lower age (45.2±9.1 years) and lower BMI (26.7±4.2 kg/m²), which may explain the higher prevalence reported in the present analysis (Table 3). The information gathered here from KIMS can also be compared with data made available from other GHD surveillance databases (31). One such prevalence study has been performed according to the NCEP criteria on a total of 2531 patients, of which 1115 were Europeans.

Table 3 MetS prevalence according to NCEP criteria in studies of patients with GHD deficiency.

<table>
<thead>
<tr>
<th>Refs</th>
<th>Country</th>
<th>n</th>
<th>Type</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>MetS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(30)</td>
<td>The Netherlands</td>
<td>50</td>
<td>AO</td>
<td>45.2</td>
<td>26.7</td>
<td>38.0</td>
</tr>
<tr>
<td>(31)</td>
<td>Europe</td>
<td>1115</td>
<td>AO</td>
<td>50.1</td>
<td>28.4</td>
<td>35.6</td>
</tr>
<tr>
<td>(31)</td>
<td>Europe</td>
<td>305</td>
<td>CO</td>
<td>29.5</td>
<td></td>
<td>14.5</td>
</tr>
<tr>
<td>(31)</td>
<td>USA</td>
<td>984</td>
<td>AO</td>
<td>52.8</td>
<td>31.8</td>
<td>59.4</td>
</tr>
<tr>
<td>This study</td>
<td>Europe</td>
<td>2479</td>
<td>AO</td>
<td>49.5</td>
<td>29.0</td>
<td>43.1</td>
</tr>
</tbody>
</table>

CO, childhood-onset; AO, adult-onset.
with adult-onset GHD. An age-adjusted MetS prevalence of 35.6% was found, a figure slightly lower than in this study. By contrast, patients from the United States had a much higher BMI and prevalence of MetS. Differences in prevalence of MetS between studies in GHD patients are therefore at least partially explained by baseline differences in age, BMI, age of onset, and/or country of origin (Table 3). 

This study also extended the knowledge about the presentation and characteristics of MetS in GHD. First, it showed that age in GHD, similar to the general population, has a major impact on MetS prevalence, but with a different expression depending on gender (32, 33). Males were affected at a younger age, possibly by an earlier weight gain and increase in blood pressure, while females developed MetS mainly after menopause, finally reaching a higher prevalence than males. In comparison with the DECODE study, a similar gender-related pattern was observed with a clear shift toward a higher MetS prevalence in the GHD cohort (25). In addition, and as observed in the general population, the analysis showed the pronounced impact of BMI and waist circumference upon the prevalence and the prevalence ratio of MetS (34, 35). BMI values exceeding 30 and 35 kg/m², respectively, were associated with a MetS prevalence of more than 60 and 70%, respectively, and a MetS prevalence ratio over 4.0 and 5.0 respectively. A waist circumference above 106 cm in males and 92 cm in females was associated with a MetS prevalence around 60% and a MetS prevalence ratio over 4.0 and 5.0 respectively. A waist circumference above 106 cm in males and 92 cm in females was associated with a MetS prevalence around 60% and a MetS prevalence ratio over 4.0 and 5.0 respectively. In accordance with the definitions, the MetS prevalence ratio for waist circumference categories in IDF was lower than in NCEP, but still showed a progressive increase by category. The high prevalence of the individual MetS components in GHD patients also affects the positive predictive value compared with the population data from the DECODE study (25). Moreover, argumentation can be developed to assign a major role for GHD in the development of MetS. While the severity of GHD, expressed by IGF1 SDS, had no impact on the MetS prevalence, both GHD duration and isolated GHD without other pituitary deficiencies were significantly associated with an increased occurrence of MetS. The finding is a recurring argument to view isolated GHD as an entity necessitating adequate GH replacement (36). Finally, the classification of MetS components into escalating MetS categories not only confirmed the influence of age and BMI upon the development of MetS, it also allowed to demonstrate the importance of the number of components when waist circumference, blood pressure, HDL-cholesterol, and triglycerides were adjusted for age, gender, and BMI. The increasing number of components was clearly accompanied by more adverse changes in the different components, suggesting that the more components aggregated the more complications could be expected.

Moreover, this study attempted to quantify the comorbidities associated with MetS in GHD patients. In the general population MetS was accompanied by a four- to five-fold increase in diabetes mellitus (37) and a 1.5- to 2-fold increase in cardiovascular disease (38, 39). A similar pattern has been observed in the present analysis, since the prevalence ratio for diabetes was 4.65, for cardiovascular diseases 1.91, and for cerebrovascular disease 1.77 when comparing the MetS group with the noMetS group. The escalating MetS categories further demonstrated the impact of clustering of the components upon the prevalence of the different comorbidities, showing the highest occurrence when four or all five components were present.

In view of the risk of premature cardiovascular death in hypopituitary patients on conventional hormone therapy without GH replacement, the finding of a high MetS prevalence draws attention to the fact that hypopituitary patients with GHD not only need adequate hormone replacement therapy including GH therapy, but also puts a focus on their metabolic problems. This includes correction of overweight by intensifying weight management and by stimulating physical activity. Medication to correct dyslipidemia, insulin resistance, and hypertension should not be delayed when cardiovascular risk factors persist despite lifestyle modification.

Declarations of interest
A F Mattsson and M Kolowska-Håggeström are permanent employees of Pfizer Health AB, Sweden; A Luger and R Abs are members of the KIMS Strategic Advisory Board; J Verhelst and M I Göth are members of the KIMS International Board; and M Thunander has nothing to disclose.

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